REMARKS

In the Claims:

Claims 113, 136, and 137 are cancelled herein without disclaimer or prejudice to pursuing the inventions of claims 113, 136, and 137 in a continuing application. Claims 112 and 115 are amended herein to clarify that the method of claims 112 and 115 is useful for treating a vascular injury, stenosis, restenosis, atherosclerosis, thrombosis, or rethrombosis. No new matter is added by this amendment. Support for the amendment may be found at pages 2-4, 8, 11, and 27 of the specification.

35 U.S.C. § 112, first paragraph – Enablement

Claims 109-119 and 121-142 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Office action states four bases for this rejection.

First, the Office action states that the declaratory evidence does not enable the breadth of the pending claims because this declaratory data is based on the p27 protein, which allegedly was not known in 1989, the effective filing date of the present application.

Second, the Office action states that even if Applicants could rely on the declaratory data, the claims still are not enabled because they are overly broad. In particular, the Office action alleges that the diseases listed in the specification and specifically recited in the claims have substantially different etiology than injury induced neointimal hyperplasia (the condition treated by the procedure described in the declarations), and are likely caused by substantially different factors, both genetic and environmental.

Third, although the Office action acknowledges that the specification discloses a number or putative therapeutic proteins that could be used in the claimed methods, the Office action asserts that this disclosure is not enabling because

"no data regarding the actual activity of these putative therapeutic proteins when expressed *in vivo* according to the instant methods has been presented."

Fourth, the Office disputes the relevancy of the references cited by Applicants as further evidence demonstrating that the present invention is enabled. Specifically, the Office action states that the cited references "do not add to the guidance provided by the specification regarding site specific instillation of transformed vascular cells." (Office action mailed May 19, 2005, p. 9).

Applicants respectfully disagree and maintain that the enablement requirement is satisfied. To overcome an enablement rejection, an applicant is required to demonstrate, by argument or other evidence, that the disclosure *as filed* would have enabled the claimed invention. *See* MPEP § 2164.05. Applicants respectfully maintain that the specification, as filed, enables one of ordinary skill in the art to practice the claimed invention. Further, in accordance with the MPEP's allowance of submission of a declaration showing enablement of a claimed invention after the filing date of an application (MPEP § 2164.05), Applicants previously submitted a first Nabel Declaration and herein submit a second Nabel Declaration, both of which demonstrate enablement as of the filing date.

More specifically, in accordance with the requirements of MPEP § 2164.06, on July 30, 2003, Applicants submitted a first Declaration of Elizabeth G. Nabel, M.D., (hereinafter the "first Nabel Declaration"). As discussed previously, the first Nabel Declaration recites the successful application of the claimed method. In particular, at paragraphs 7-9, the first Nabel Declaration describes using the procedures outlined at pages 14-16 of the specification to implant a cell transformed to express the p27 protein into a mammal. This procedure achieved the therapeutic effect of "significant reduction in intimal hyperplasia and arterial lesion development." (First Nabel Declaration, para. 10). The Office action rejects this data because it is based on use of the p27 gene. According to the Office action, "[t]he p27 gene was not known in the prior art as of the 1989 filing

date. . . . Thus, the material used in the experiments described in the declaration was not described in the specification or well known to one of skill in the art."

Applicants respectfully disagree that the data submitted in the first Nabel Declaration should be rejected because it is based on use of the p27 therapeutic protein. Indeed, the broadest claimed method is not limited to use with any specific protein. Therefore, in demonstrating that the *claimed method* invention is enabled, Applicants are neither required to use, nor limited to using, only those proteins disclosed in the specification, or those known in the art at the time the application was filed. Thus, Applicants maintain that the first Nabel Declaration adequately demonstrates that the claimed invention is enabled. In any event, solely for reasons related to expediting allowance of the claims, Applicants herein submit a second Nabel Declaration.

In the second Nabel Declaration, the inventor repeated the experiments outlined at pages 14-16 of the specification but this time used a therapeutic protein that both is disclosed in the specification and was known in the art at the time of filing, basic fibroblast growth factor ("bFGF"). In particular, paragraphs 7-10 of the second Nabel Declaration state the following:

> 7. Six pigs, three as a control group and three as an experimental group, were used. In each pig, VSMCs were isolated from a peripheral vein and grown in cell culture. The cultured VSMCs from three pigs were transformed with an adenoviral vector expressing basic fibroblast growth factor (bFGF). The cultured VSMCs from the three control pigs were transformed with a control adenoviral vector that does not express a biologically active protein (AdCo). Four days after transformation, the cells were examined by immunostaining for bFGF and Western blotting, which confirmed that the AdbFGF cell lines expressed bFGF and the cell lines in the control group did not.
>
> 8. Thereafter, the transformed VSMCs were site-specifically instilled into the pigs. Each of the six pigs was anesthetized and the femoral arteries were exposed. A balloon angioplasty catheter was introduced into each femoral artery, and the balloon was inflated to create a vascular injury. Following vascular injury of each artery, each arterial segment was flushed with saline, and 4.5×10^6 transformed VSMCs were instilled therein at the site of injury. The transformed VSMCs originated from the pigs in which they were implanted.

> 9. The pigs were allowed to recover for three weeks. Following the recovery period, the pigs were anesthetized, the arterial segments were removed from each pig, and the pigs were euthanized. The arterial segments were fixed and analyzed.
>
> 10. Analysis of the arterial segments revealed that the three experimental pigs, with VSMCs expressing bFGF, had a significant reduction in intimal hyperplasia and arterial lesion development as compared to the three control pigs.

(Second Nabel Declaration, paragraphs 7-10, submitted August 19, 2005). Thus, Applicants now have submitted declaratory evidence, based on expression of a therapeutic protein, bFGF, which was *known* at the time of filing *and* disclosed in the specification, that the claimed method was enabled as of the filing date. Indeed, this declaratory evidence demonstrates that the claimed method achieves the therapeutic effect of "reduction in intimal hyperplasia and arterial lesion development."

Significantly, based on both Nabel Declarations and the information provided in the specification, Applicants have provided evidence that instillation of cells transformed to express a marker gene according to the claimed method successfully achieves expression of a marker gene for at least 6 weeks (see page 35 of the specification); that instillation of cells transformed to express the therapeutic protein bFGF achieves the therapeutic effects of reducing neointimal hyperplasia (0.23$\pm$ 0.033 for AdvbFGF compared to 0.51 $\pm$ 0.037 for the control group) and arterial lesion development; and that instillation of cells transformed to express the therapeutic protein p27 also achieves the therapeutic effects of reducing neointimal hyperplasia (0.58$\pm$0.17 Advp27 compared to 1.61$\pm$0.29 for the control group) and arterial lesion development. Thus, the specification combined with the declaratory data provides significant evidence that the claimed method was enabled as of the filing date of this application.

Further, neither *treating* a disease nor *achieving* a therapeutic effect is a limitation of claims 109-114. Rather, claims 109-114 merely require that the method achieve *expression* of the protein the instilled cells were transformed to express. In particular, claims 109-114 require that the claimed method achieve

expression of the following proteins: tissue plasminogen activator, urokinase, streptokinase, transforming growth factor alpha, transforming growth factor beta, angiogenin, tumor necrosis factor alpha, tumor necrosis factor beta, acidic fibroblast growth factor, and basic fibroblast growth factor), a protein that induces angiogenesis, a protein that induces revascularization, a protein that is useful for treating an ischemic condition, or a protein that improves vascular or cerebrovascular circulation.

Applicants have provided substantial evidence demonstrating that the claimed method is enabled for achieving *expression* of a variety of proteins, each of which has different biological properties and activities. Specifically, as discussed above, at pages 31-41, the specification demonstrates enablement of using the claimed method to achieve expression of the marker gene β-galactosidase. The first Nabel Declaration demonstrates that the specification enables one of ordinary skill in the art to achieve expression of a therapeutic protein that is a cell-cycle inhibitor, p27. The second Nabel Declaration demonstrates that the specification enables one of ordinary skill in the art to achieve expression of another therapeutic protein, bFGF. Thus, Applicants have provided evidence that three different proteins, with different biological activities and properties, can be expressed *in vivo* according to the method of claims 109-114. There is no reason to suspect that one of ordinary skill in the art would not be able to follow the teachings of the specification to achieve expression of any of the proteins identified in claims 109-114. Therefore, the enablement requirement is satisfied for these claims because "[a]ll that is necessary [to satisfy the enablement requirement] is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art." MPEP § 2164.08.

Even further, the enablement requirement for all of the claims is satisfied because the scope of claims 109-119, and 121-142 bears a reasonable correlation to the scope of enablement. According to the MPEP, a "reasonable correlation" is all that is required. MPEP § 2164.08. *See also In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). As amended, the claims are

directed to treatment of a vascular injury, stenosis, restenosis, atherosclerosis, thrombosis, or rethrombosis. Each of these conditions involves common attributes, such as obstruction or narrowing of a blood vessel.

Indeed, as explained in the specification, for example, atherosclerosis, vascular injury, and restenosis share common cellular events including ""endothelial [cell] injury and release of potent growth factors by activated macrophages and platelets," and promotion of "platelet aggregation and thrombus formation . . . release of mitogens from platelets and macrophages, smooth muscle cell proliferation and monocyte infiltration." See page 3 of the specification. Thus, there is a nexus between the etiology of the conditions recited in the claims and the evidence of enablement provided by the specification and the first and second Nabel Declarations.

In particular, the specification, as well as the first and second Nabel Declarations teach that a blood vessel which is narrowed or obstructed, for example by an atherosclerotic plaque or proliferation of white blood cells or smooth muscle cells, may be treated by instilling syngeneic cells transformed to express a therapeutic protein, such as p27 or bFGF. The specification provides evidence that one of ordinary skill in the art may follow the teachings therein (pages 31-41) to achieve expression (for at least six weeks) of a protein encoded by a cell transformed to express that protein in the area surrounding the site of instillation of the transformed cell. The first and second Nabel Declarations provide declaratory evidence that following the teachings of the specification, the inventor was able to successfully instill cells transformed to express either p27 or bFGF. As discussed above, expression of bFGF achieved a reduction in neointimal hyperplasia of 0.23 ± 0.033 compared to control (0.51 ± 0.037) while expression of p27 achieved a reduction of 0.58 ± 0.17 compared to control (1.61 ± 0.29). Thus, Applicants have demonstrated that expression of two different therapeutic proteins, according to the claimed methods, resulted in the therapeutic effects of reducing neointimal hyperplasia and arterial lesion development.

There is a nexus between this evidence and the conditions to be treated recited in the claims because the evidence demonstrates that one type of vascular injury, *i.e.* arterial lesion development, is treated by the claimed method. Additionally, there is a nexus because neointimal hyperplasia and arterial lesion development may cause or contribute to the other conditions recited in the claims: stenosis, restenosis, thrombosis, and rethrombosis. Thus, based on the teachings of the specification, and the declaratory evidence demonstrating enablement of using the claimed method to treat neointimal hyperplasia and arterial lesion development, one of ordinary skill in the art would be enabled to practice the full scope of the invention as claimed herein.

Further, the specification teaches one of ordinary skill in the art which of the therapeutic proteins recited in claims 109 and 115 may be used to treat the diseases recited in the claims. In particular, at page 27 the specification teaches that tPA, urokinase, and streptokinase may be used in the treatment of thrombosis or rethrombosis while transforming growth factor-alpha, transforming growth factor-beta, angiogenin, tumor necrosis factor-alpha, tumor necrosis factor-beta, acidic fibroblast growth factor and basic fibroblast growth factor can be used to cause revascularization and/or to treat an ischemic organ. One of ordinary skill in the art will appreciate vascular injury, stenosis, restenosis, atherosclerosis, thrombosis, and rethrombosis all may cause an organ to be ischemic. Even further, the second Nabel Declaration provides evidence that bFGF achieves the therapeutic effect of reducing neointimal hyperplasia and arterial lesion development *in vivo* when used in the claimed methods. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP § 2164.01(b) (citations omitted).

Although Applicants respectfully disagree with the Office's objection to Applicants' reliance on references cited by Applicants in the Response and

Request for Reconsideration mailed May 25, 2004, Applicants respectfully submit that in view of the additional declaratory evidence provided herein (the second Nabel Declaration), art references are not needed to further demonstrate that the specification enables one of ordinary skill in the art to practice the claimed invention.

At least for the reasons stated above, the claims as amended herein are not overly broad and undue experimentation would not be required to practice the full scope of the invention as claimed. Applicants have overcome the bases for rejecting the presently pending claims for alleged lack of enablement. Therefore, Applicants respectfully request this ground of rejection be withdrawn.

Double Patenting

The Examiner maintains that the rejection of claims 106-109, 114-118, 121-131, 136, and 142-146 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of U.S. Patent No. 6,203,991.

Applicants respectfully disagree with this ground of rejection, but as stated previously, to expedite allowance of the pending claims, Applicants will file a terminal disclaimer upon the allowance of the rejected claims.

CONCLUSION

Pending claims 106-108, and 120 are allowable. Applicants respectfully submit that pending claims 109-112, 114-135, and 138-146 also are patentable. Applicants respectfully request the Examiner grant allowance of these claims. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of these claims.

Respectfully Submitted,

C. Noel Kaman

C. Noel Kaman
Reg. No. 51,857
Attorney for Applicant

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312)321-4200